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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Applicati n No.	Applicant(s)	
	09/720,583	POUWELS ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 March 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *1-27 and 30-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The Response filed on March 14, 2003, as paper No. 12, is acknowledged. Amendment to claims and specification has been entered as requested. Claim 28 is amended; claim 29 is deleted. New claim 39 is entered. Claims 1-39 are pending. Claims 28 and 29 are the subject of this Office Action; claims 1-27 and 30-39 are withdrawn from consideration as directed to the non-elected invention.

Detailed Office Action

1. Objections

Because the specification has been amended the objections made in the previous Office Action, paper No. 11 have been withdrawn.

New claim 39 is objected to as depending on claim 2 withdrawn from consideration as directed to the nonelected invention. For examination purposes it is assumed that the claim is dependent on claim 28.

2. Rejections

2.1. 35 USC, section 101

Rejection of claim 28 under 35 U.S.C. 101 made in the previous Office Action, paper No. 11, is withdrawn because the claim has been amended.

2.2. 35 USC, section 112, second paragraph

Rejection of claim 28 under 35 U.S.C. 112, second paragraph, made in the previous Office Action, paper No. 11 is withdrawn, because the claim has been amended.

The amended claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the phrase "assisting in the production of vitamin B_{12}", which is vague and confusing and not defined by the claim or by the specification. This phrase renders the claim indefinite. The examiner suggests the following language: "gene of *Propionibacterium* belonging to vitamin B_{12} biosynthesis pathway".

In addition, claim 28 is directed to production of vitamin B_{12} by *Propionibacterium* having a plasmid comprising a origin of replication in SEQ ID NO: 1 or its fragment contained between SalI and AlwNI restriction sites (nucleotides 1 - 1800 of SEQ ID NO: 1); part a) and b) of the claim. However, the claim is confusing in recitation of DNA fragments c), d) and e) that have no ability to originate replication, because they do not contain the replication origin of the p545 plasmid. Thus, DNA fragments c), d) and e) cannot be maintained within *Propionibacterium*.

Claim 39 is rejected as depending on the rejected base claim.

2.3. 35 USC, section 112, first paragraph

3.3.1. Biologic deposit requirement

Rejection of claim 28 made in the previous Office Action is withdrawn, because

of the amendment the rejection is not pertinent.

The examiner acknowledges the attorney statement concerning public availability of the biologic deposit made under the terms of Budapest treaty.

2.3.2. Lack of written description

Claim 28 and 39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 28 is directed to a process for production of vitamin B_{12} (cobalamin), comprising culturing a *Propionibacterium* host cell containing a polynucleotide:

(a) SEQ ID NO: 1 or the complement thereof,

(b) a sequence from SEQ ID NO: 1 that corresponds to either the 1.7.kb fragment of SEQ ID NO: 1 delineated by restriction sites Sal 1 and AlwN1 or nucleotides 1- 1800 of SEQ ID NO: 1;

(c) a sequence that encodes a polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3 or a polypeptide at least 70 % homologous thereto, the latter polypeptide having the activity of the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3;

(d) a sequence according to (c) that is a fragment from SEQ ID NO: 1 corresponding to positions 273-1184 or a fragment from SEQ ID NO: 1 corresponding to position 1181 to 1438; or

(e) a sequence that is at least 70% homologous to a sequence as defined

under (a),

(b) or (d), over a region of at least 100 contiguous nucleotides;

and a sequence that is an endogenous gene of a *Propionibacterium* assisting in the production of vitamin B_{12} operatively linked to a control sequence, which is capable of providing for expression of the gene. The claim is lacking written description of the activity of SEQ ID NO: 2 or SEQ ID NO: 3 and the specification is silent about this activity. The specification is also silent about the structure of any polypeptide that is 70% homologous to SEQ ID NO: 2 or 3, and even if that structure were disclosed the function is unknown, because the function of SEQ ID NO: 2 and 3 is not disclosed by Applicants. The claim is also lacking written description, because Applicants failed to disclose any portion of SEQ ID NO:2 or 3 or fragment of SEQ ID nO:1 or variants thereof which is capable of providing for replication of heterologous gene within *Propionibacterium*, wherein the sequence is other than that of SEQ ID NO: 1 or its fragment consisting of nucleotides 1-1800. The Applicants write, "The heterologous or endogenous gene may be inserted between nucleotides 1 and 200 or between nucleotides 1500 to 3555 of SEQ ID NO: 1 [complete nucleotide sequence of the p545 plasmid, MW]"(page 10, line 22). Therefore, they used in construction of their plasmid pBRES36COB nucleotides 1-1800 of SEQ ID NO: 1 containing p545 plasmid replication origin and the *cobA* (uroporphyrinogen III methyltransferase) gene from *Propionibacterium freudenreichii.* Applicants did not link operationally the cobA, or other gene, to any other replication origin than the fragment of SEQ ID NO: 1. The specification does not contain any disclosure of the function of all plasmids within the

genus of claimed method, and the vast majority of such plasmids would be unable to encode a vitamin B_{12} biosynthetic gene as they lack any functional replication origin and thus would be lost on growth of the bacterial culture. As many functionally unrelated plasmids are recited in the claimed methods, the single disclosed plasmid is not representative of the genus of plasmids within the claimed methods. Therefore, one cannot reasonably conclude that Applicants had possession of the of the attributes and features of all claimed methods.

3.3.4. Scope of enablement

Claim 28 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *Propionibacterium* cells transformed with the pBRES36COB vector or with p545 plasmid wherein cobA gene is inserted between nucleotides 1 and 200 or between nucleotides 1500 to 3555 of said plasmid, does not reasonably provide enablement for a polynucleotide comprising a polynucleotide consisting of:

(1) any sequence that encodes a polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3 or a polypeptide at least 70 % homologous thereto, the latter polypeptide having the activity of the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3;

(2) any sequence according to (1) that is a fragment from SEQ ID NO: 1 corresponding to positions 273-1184 or a fragment from SEQ ID NO: 1

corresponding to position 1181 to 1438;

(3) any sequence that is at least 70% homologous to SEQ ID NO: 1 or complement thereof;

(4) any sequence that is in 70% homologous to a sequence from SEQ ID NO: 1 that corresponds to either the 1.7 kb fragment of SEQ ID NO: 1 delineated by restriction sites Sal 1 and AlwN1 or nucleotides 1-1800 of SEQ ID NO: 1; or

(5) any sequence that is at least 70% homologous to a sequence as defined under (1), (2) or (4), over a region of at least 100 contiguous nucleotides,

and a gene of *Propionibacterium* assisting in the production of vitamin B_{12} operatively linked to a control sequence, which is capable of providing for expression of the gene.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of the claim is not in accordance with the scope of enablement; see the above rejection for lack of written description. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the

predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses production of vitamin B_{12} by culturing *Propionibacterium* containing any sequence from natural and/or man-made source, wherein the sequence comprises:

(1) any sequence that encodes a polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3 or a polypeptide at least 70 % homologous thereto, the latter polypeptide having the activity of the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3;

(2) any sequence according to (1) that is a fragment from SEQ ID NO: 1 corresponding to positions 273-1184 or a fragment from SEQ ID NO: 1 corresponding to position 1181 to 1438;

(3) any sequence that is at least 70% homologous to SEQ ID NO: 1 or complement thereof;

(4) any sequence that is in 70% homologous to a sequence from SEQ ID NO: 1 that corresponds to either the 1.7 kb fragment of SEQ ID NO: 1 delineated by restriction sites Sal 1 and AlwN1 or nucleotides 1-1800 of SEQ ID NO: 1; or

(5) any sequence that is at least 70% homologous to a sequence as defined under (1), (2) or (4), over a region of at least 100 contiguous nucleotides,

and a gene of *Propionibacterium* assisting in the production of vitamin B_{12} operatively linked to a control sequence, which is capable of providing for expression of the gene.

The specification provides an enablement (Example 5) how to produce vitamin B_{12} by culturing *Propionibacterium freudenreichii* ATCC6207 transformed with the vector named pBRES36COB containing p545 plasmid sequence controlling replication, and the *cobA* (uroporphyrinogen III methyltransferase) gene from *Propionibacterium freudenreichii.* Thus, the scope of claim is limited to transformants of *Propionibacterium* that contains the *cobA* or other gene of vitamin B_{12} biosynthetic pathway operably linked to replication controlling element from plasmid p545. The specification is lacking any teaching of an origin of replication within:

(1) a sequence that encodes a polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3 or a polypeptide at least 70 % homologous thereto, the latter polypeptide having the activity of the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3;

(2) a sequence according to (1) that is a fragment from SEQ ID NO: 1 corresponding to positions 273-1184 or a fragment from SEQ ID NO: 1 corresponding to position 1181 to 1438;

(3) a sequence that is at least 70% homologous to a sequence over a region of at least 100 contiguous nucleotides of any of SEQ ID NO:1-3.

Futhermore, Applicants have failed to define what are the necessary structural features of nucleotides 1-1800 of SEQ ID NO: 1 that provide for its activity of an origin of replication in *Propionibacterium.*

Applicants failed to disclose a sequence of *Propionibacterium,* which is capable of providing for replication of a heterologous gene within *Propionibacterium*, wherein the

sequence is other than that of SEQ ID NO: 1 or its fragment consisting of nucleotides 1-1800. The Applicants write, "The heterologous or endogenous gene may be inserted between nucleotides 1 and 200 or between nucleotides 1500 to 3555 of SEQ ID NO: 1 [complete nucleotide sequence of the p545 plasmid, MW]"(page 10, line 22). Therefore, they used in construction of their plasmid pBRES36COB nucleotides 1-1800 of SEQ ID NO: 1 containing p545 plasmid replication origin and the *cobA (*uroporphyrinogen III methyltransferase) gene from *Propionibacterium freudenreichii.* Applicants did not link operationally the cobA, or other gene, to any other replication origin than the fragment of SEQ ID NO:1.

The specification does not give examples or guidance as to the structure of replication origin that would be suitable for replicating and contained in

(1) a sequence that encodes a polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3 or a polypeptide at least 70 % homologous thereto, the latter polypeptide having the activity of the polypeptide of SEQ ID NO: 2 or SEQ ID NO: 3;

(2) a sequence according to (1) that is a fragment from SEQ ID NO: 1 corresponding to positions 273-1184 or a fragment from SEQ ID NO: 1 corresponding to position 1181 to 1438;

(3) a sequence that is at least 70% homologous to SEQ ID NO: 1 or complement thereof;

(4) a sequence that is 70% homologous to a sequence from SEQ ID NO: 1 that corresponds to either the 1.7 kb fragment of SEQ ID NO: 1 delineated by restriction sites Sal 1 and AlwN1 or nucleotides 1-1800 of SEQ ID NO:

1; or

(5) a sequence that is at least 70% homologous to a sequence as defined under (1), (2) or (4), over a region of at least 100 contiguous nucleotides,

and thus could be linked to one or more vitamin B_{12} biosynthesis genes to provide for vitamin B_{12} production.

Without further guidance as to the structure of the replication origin that may be used, probability of success in making the claimed invention is very low, and the experimentation left to those skilled in the art improperly extensive and undue.

Claim 39 is included in this rejection as depending on the rejected claim 28.

2.4. 35 USC section 102

Rejection of claim 29 made under 35 U.S.C. 102(b) as being anticipated by the US Patent No. 5,545,538 (the patent) issued on August 13, 1996 to Ashai S. et al. is moot because the claim has been cancelled.

3. Conclusion

No claim is in conditions for allowance, but claim 28 contains allowable subject matter for reasons indicated in the previous Office Action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00

a.m. to 4:30 p.m. If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

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